IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

In re application of: Armitage, et al.

Application No.: 09/673,074

Filed: February 26, 2001

Title: OCULAR IRRIGATING SOLUTION

Attorney Docket No.: HASLP004, HL52257/002/GW/eg

Examiner: FAY, ZOHREH A

Group: 1614

AFFIDAVIT UNDER 37 CFR 1.132

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

I William John Armitage declare as follows:

1. I was awarded a doctorate of Philosophy degree in Cryobiology in 1979 by the Council for National Academic Awards for research carried out in the Medical Research Council's Clinical Research Centre in Harrow, London. After receiving my PhD, I worked for the Medical Research Council in the Medical Cryobiology Group, Department of Surgery, Cambridge, UK. After a postdoctoral fellowship in the Biology Division at Oak Ridge National Laboratory, Tennessee, I returned to Cambridge for two years before taking a position in the Department of Ophthalmology, University of Bristol in 1984. My main area of research has been the preservation of cells and tissues for transplantation, including cornea, heart valve, blood vessels, blood cells, cord blood and heart. Since moving to Bristol to set up the Bristol Eye Bank, which is now one of the largest eye banks in Europe, I have also carried out research into corneal transplant immunology and the long-term survival of corneal grafts. I have more than 60 articles in refereed scientific journals and a further 60 publications (book chapters, conference proceedings, editorials, conference abstracts). I hold appointments in the University of Bristol as Director of Tissue Banking and as Professorial Research Fellow in Tissue Biology and Transplantation.

2. I am a co-inventor of the subject matter described and claimed in the above-identified patent application. The patent application describes and claims compositions and methods for irrigating the eye of a patient during surgery. As explained in the subject patent application, the compositions have various benefits such as being free of heat-labile components that might be oxidised during sterilization.

3. My research into corneal preservation over the past 20 years in Bristol has required a significant understanding of corneal physiology and cell biology and has involved extensive use of corneal perfusion techniques and measurement of corneal endothelial function, which have a direct bearing on the above referenced US patent application. Previous research into the development of perfusion solutions for heart preservation also contributed background and expertise in the maintenance of cell and tissue viability using synthetic media.

4. I understand that the Patent Examiner responsible for examining our above-referenced patent application has rejected the application based upon primarily US Patent No. 4,725,586 issued to Lindstrom et al. (Lindstrom). I have reviewed the Lindstrom patent and found that it describes irrigating compositions, each of which require at least a source of electrolytes in the form of a balanced salt solution, chondroitin sulphate, HEPES buffer, and 2-mercaptoethanol. The claims of my above-identified patent application cover irrigating solutions and methods of irrigating employing solutions that contain no material amounts of either chondroitin sulphate or 2-mercaptoethanol.

I also understand that the Patent Examiner has maintained a rejection of our claims on the basis that we have not presented experimental evidence to show that our claimed invention would function differently if 2-mercaptoethanol or chondroitin sulphate were added to our composition. The purpose of this declaration is to provide the experimental evidence showing this.

5. Our claimed invention can be used as a single-part solution that maintains corneal endothelial function and which can be sterilized by autoclaving. The latter is an important feature given that the irrigating solutions are commonly supplied in 500-ml volumes and that sterilization of such large volumes by filtration is not an acceptable process for solutions intended for clinical use.

Based on my reading of the Lindstrom patent, I understand the patent to require 2-mercaptoethanol and chondroitin sulphate as essential components. I believed that one or both of these components may be heat labile, precluding the option of sterilization by autoclaving. If that turned out to be the case, these components would be detrimental to our irrigating solution.

6. To confirm my belief, we prepared a representative example of the claimed irrigating solution with and without 2-mercaptoethanol and chondroitin sulphate, and then autoclaved the solutions and compared the outcome. A significant change in colour of the solution containing 2-mercaptoethanol and chondroitin sulphate indicated that one or both of the additional components required in the Lindstrom patent were heat labile. This demonstrates that these constituents are detrimental to our claimed irrigating solution, as they would preclude sterilization by autoclaving.

The experimental methodology used to confirm my belief is described in the attached Exhibit A. Briefly, we prepared one solution conforming to our claimed composition and another solution that was identical except for the addition of 2-

mercaptoethanol and chondroitin sulphate. We called the solution corresponding to our claims UB-M4 and the solution with the 2-mercaptoethanol and chondroitin sulphate UB-M4L. Note that the physiologically acceptable organic buffer and source of bicarbonate ions recited in the claims were provided as Hepes buffer and sodium bicarbonate, respectively.

Because the presence of 2-mercaptoethanol and chondroitin sulphate in an irrigating solution that otherwise conformed to our claimed solution rendered the solution unsuitable for autoclaving, I conclude that the claimed composition functions differently with 2-mercaptoethanol and chondroitin sulphate added. Therefore, I also conclude that the addition of such agents to the claimed composition materially alters the effectiveness of our claimed composition.

7. I declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 30 Sept 2005 Signature W.J. Armitage

William John Armitage, PhD

Methods

1. All chemical constituents were AnalaR grade or better. The water was purified by reverse osmosis and a deionising column.

2. The composition of UB Solution (version UB-M4) is given in Table 1.

3. The composition of UB-M4L containing 2-mercaptoethanol (1 mM) and chondroitin sulphate (5% w/v) is given in Table 2. These concentrations are the upper limits of the respective concentration ranges specified in the Lindstrom patent.

4. One litre of each composition was prepared and dispensed into 500-ml glass DIN bottles. The bottles were closed with 32-mm rubber stoppers held in place by aluminium crimped caps.

5. The solutions were autoclaved in an NHS manufacturing pharmacy unit at 121°C for 15 minutes. These are standard conditions for the sterilization of liquids for infusion and clinical use.

Results

Appearance of the solutions:

	UB-M4	**UB-M4L**
Before autoclaving	Clear, colourless liquid	Clear, very pale yellow liquid
After autoclaving	Clear, colourless liquid	Clear, brown liquid

Table 1. Composition of UB-M4

Compound	Formula		Formula weight	Composition mmol/l	g/l
Sodium chloride	NaCl		58.44	125.60	7.34
Potassium chloride	KCl		74.55	5.37	0.40
Calcium chloride	$CaCl_2.6H_2O$	1 mol/l solution	219.08	0.625	0.625 ml
Sodium phosphate, dibasic	Na_2HPO_4		141.96	0.77	0.11
Sodium bicarbonate	$NaHCO_3$		84.01	15.00	1.26
Hepes buffer (free acid)	$C_6H_{18}N_2O_4S$	1 mol/l solution	238.30	20.00	20.0 ml
Water					ad 1000 ml

Table 2. Composition of UB-M4L containing Lindstrom's essential constituents.

Compound	Formula		Formula weight	Composition mmol/l	g/l
Sodium chloride	NaCl		58.44	125.60	7.34
Potassium chloride	KCl		74.55	5.37	0.40
Calcium chloride	$CaCl_2.6H_2O$	1 mol/l solution	219.08	0.625	0.625 ml
Sodium phosphate, dibasic	Na_2HPO_4		141.96	0.77	0.11
Sodium bicarbonate	$NaHCO_3$		84.01	15.00	1.26
Hepes buffer (free acid)	$C_6H_{18}N_2O_4S$	1 mol/l solution	238.30	20.00	20.0 ml
Chondroitin sulphate				5%	50.00
2-Mercaptoethanol	C_2H_6OS	Liquid	78.13	1.00	70 µl
Water					ad 1000 ml